CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
NITRAPYRIN

SB 950-272, Tolerance # 350
Chemical Code #: 000439

July 29, 1986
Revised: 10/20/86; 2/13/87; 6/10/88; 4/9/90; 6/5/92; 11/15/94, 12/8/97

I. DATA GAP STATUS

Combined (chronic & oncogenicity) rat:	No data gap, possible adverse effect
Chronic dog:	No data gap, no adverse effect
Onco mouse:	No data gap, possible adverse effect
Repro rat:	No data gap, no adverse effect
Terato rat:	No data gap, possible adverse effect
Terato rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotox:	Not required at this time

The EPA requested toxicity testing for nitrapyrin (010 040028, Guidance for the Reregistration of Pesticide Products Containing Nitrapyrin, EPA, June, 1985). Some of the studies submitted were conducted with 6-chloropicolinic acid, a metabolite for both plants and animals (004 943453 and 943526) and are considered to be supplemental. Supplemental studies are not used to fulfill SB-950 data requirements.

NOTE: Toxicology one-liners are attached.
** indicates acceptable study.
Bold face indicates possible adverse effect
Summary prepared and revised 10/20/86, 2/13/87 and 6/10/88 by J. Gee; 4/90 by M. Silva, 9/20/90 by M. Silva and H. Green, 6/5/92; M. Silva, 11/15/94; J. Gee, 12/8/97.
FILE NAME: T971208
Files reconciled through volume # 350-042, Record # 156915. These pages contain summaries only. Individual worksheets may contain additional effects and should be reviewed.

II. TOXICOLOGY SUMMARY

COMBINED, RAT

Subchronic Study:

028 090540 "Nitrapyrin (N-Serve): 13-Week Dietary Toxicity Study in Fischer-344 Rats," (J.R. Szabo, B.L. Rachunek, D.C. Mensik, and C.V. Wood; The Dow Chemical Company, Lake Jackson Research Center, Freeport, TX, 8/86). Nitrapyrin technical (LOT #: 03184-122A; purity = 94.6%) was fed to Fischer-344 rats (10/sex/group) at 0 (vehicle = diet), 10, 40 and 120 mg/kg/day for 13 weeks. **Possible adverse effect.** NOEL = 10 mg/kg/day (decreased bodyweight, packed cell volume, hemoglobin and RBC counts and an increase in serum total bilirubin in both sexes at 120 mg/kg/day; increased relative and absolute kidney and liver weights at 120 mg/kg/day in both sexes; $\geq$ 40 mg/kg/day showed increased relative liver weight in both sexes and an increased absolute liver weight in males; paleness of hepatic parenchyma, vacuolation consistent with fatty change was observed in both sexes at 120 mg/kg/day and $\geq$ 40 mg/kg/day showed centrilobular hepatocyte hypertrophy; male kidneys had acute tubular necrosis and increased severity of degenerative/regenerative tubules at $\geq$ 40 mg/kg/day. Female kidneys had pigment in the proximal tubule epithelial cells at $\geq$ 40 mg/kg/day.) M. Silva, 4/27/90.

Combined Study:

**** 026 090170** "Nitrapyrin (N-Serve): Two-Year Chronic Toxicity and Oncogenicity Study in Fischer 344 Rats," (Lake Jackson Research Center, Dow, Project ID: TXT: K-031304-023, 12-26-89). Nitrapyrin technical (93.3% pure) was fed in diet to Fischer 344 rats at 0, 5, 20 or 60 mg/kg/day for 2 years (60/sex/group with 10/sex/group selected for interim sacrifice at 1 year). NOEL (males) = 5 mg/kg/day (decrease in body weight gain; increased relative and absolute kidney weights; protein droplet accumulation in the epithelial cells of the proximal convoluted tubules; increased liver weights; hypertrophy and fatty vacuolation of hepatocytes). NOEL (females) = 20 mg/kg/day (decreased body weight gain; increased absolute and relative kidney weights; increased liver weights with hypertrophy and fatty vacuolation of hepatocytes). **Possible adverse effects include primary renal tumors in males at 60 mg/kg/day and chronic progressive glomerulonephropathy in both sexes at 60 mg/kg/day. Acceptable.** M. Silva, 4/3/90.

027 087930 (supplemental to 026 090170) "The Comparative Pathobiology of α2u-Globulin Nephropathy," Swenberg, J. A., Short, B., Borghoff, S., Strasser, J. and Charbonneau, M., Toxicol. Appl. Pharmacol., 97:35-46 (1989), a review. "Studies on the pathogenesis of α2u-globulin nephropathy have demonstrated that this protein is produced in large amounts in the male rat, that reversible binding occurs between chemicals and/or their metabolites and α2u-globulin, and that this complex is resistant to proteolytic hydrolysis, leading to accumulation in renal lysosomes and subsequent cytotoxicity and cell death. This results in marked exposure-related increases in cell proliferation that persist for at least one year, providing exposure continues. This sustained increase in renal cell proliferation can promote initiated cells to form preneoplastic foci and renal neoplasia in male rats." M. Silva, 4/3/90.
027 087929 (supplemental to 026 090170) "Involvement of Reversible Binding to α2u-Globulin in 1,4-Dichlorobenzene-Induced Nephrotoxicity," Charbonneau, M., Strasser, J. Jr., Lock, E. A., Turner, M. J. Jr., and Swenberg, J.A., in: Toxicology and Applied Pharmacology, 99:122-132 (1989). Radiolabeled 1,4-[14C]-DCB (2 mmol/kg) and 1,2-[14C]-DCB (3.4 mmol/kg) was given to

Fischer 344 rats by gavage in a single dose. 1,4-DCB (similar to unleaded gasoline, which induces renal tumors in male but not female rats) and 1,2-DCB (no renal tumor inducer) were compared for their ability to bind α2U-globulin. Tests were usually performed on 3 rats/sex/group, unless otherwise specified. Urine and blood samples were taken after 24 hours. Following exanguination, liver and kidneys were removed, weighed and homogenized. Kidneys were examined histologically. Radiolabel in kidney homogenate was quantified. Column chromatography was performed to identify chemicals bound to α2u-globulin in male kidney and liver. Kidney cytosol was dialyzed in the presence or absence of SDS to demonstrate that the radiolabel was reversibly bound to α2u-globulin. A DNA assay was performed to determine cell proliferation. Protein droplets were evaluated from kidney sections (6 animals/group) by light microscopy. 1,2-DCB (a nongenotoxic isomer of 1,4-DCB) did not produce male rat-specific renal tumors at the doses tested, nor did it increase droplet formation or cell proliferation but it did bind to alpha-2u-globulin and other proteins in kidney cytosol. The amount of binding was less than for 1,4-DCB and was not entirely reversible. In addition, 1,2-DCB showed a greater potential for covalent binding to kidney, liver and plasma macromolecules than did 1,4-DCB. Therefore, at equimolar doses, 1,4-DCB induced nephrotoxicity and 1,2-DCB-induced nephrotoxicity were not the same in that 1,4-DCB showed a reversible binding to alpha-2u-globulin (in kidney), an increased protein droplet formation and cell proliferation. M. Silva, 4/3/90.

027 Supplemental information to 090170: This volume contains a letter (September 22, 1989) from G. Oliver from Dow Chemical U.S.A. to Ms. Joanne I. Miller (Office of Pesticide Programs, EPA) which discusses some preliminary findings of study 090170. There is also a letter from Dr. James E. Gibson, Director of Toxicology Affairs for The Dow Chemical Company (dated September 14, 1989) which discusses the mechanism involved in the tumorigenesis of chemicals such as Nitrapyrin in rat kidney. In addition, the mechanism is further discussed in reference to p-dichlorobenzene (Federal Register Notice, Volume 52(130)25695-25697, 1989. M. Silva, 4/3/90.

CHRONIC, RAT

006, 012 943514, 036147 "Results of Two-Year Dietary Feeding Studies of 6-Chloropicolinic Acid in Rats." (3/2/67, Dow) Metabolite, 6-chloropicolinic acid, 98.5%. Thirty/sex/group were fed 0, 1.5, 5, 15 and 50 mg/kg/day for 2 years. Unacceptable (doses not justified, inadequate initial number of animals with high mortality due to pneumonia, histopath of tissues inadequate, no diet analysis) and positive for chronic effects on liver and kidney (degenerative changes) at 0.1% (high dose). (Apostolou, 7/24/85)

004 943517, Supplemental to 943514.

CHRONIC, DOG

Subchronic Study:

028 090451 "Nitrapyrin (N-SERVE): Results of a 13-Week Dietary Toxicity Study in Dogs," (J.R. Szabo & B.L. Rachunek, Dow Chemical Co., Lake Jackson Research Center, Freeport, TX, 9/2/88.) Nitrapyrin technical (LOT #: WP860516-308B(T19B); purity = 92.8%) was fed in diet at 0 (vehicle = acetone and/or diet), 15, 40 and 75 mg/kg/day (changed on day 49 to 50 mg/kg/day, due to diet refusal) to Beagle dogs (4/sex/group) for 13 weeks. **No adverse effect indicated.** NOEL ≤ 15 mg/kg/day (decreased bodyweight and food consumption--≥ 40 mg/kg/day; brittle

haircoat and muscle wasting--75 mg/kg/day; increased absolute and relative liver weights--≥ 40 mg/kg/day and adrenal weight--75 mg/kg/day; decreased ovary and testes weights--75 mg/kg/day; progressive alterations (hypertrophy & vacuolation) of hepatic lobules--≥ 15 mg/kg/day; increased basophilic staining of proximal convoluted tubules of kidney--75 mg/kg/day). Many of the effects in this study were secondary to effects of inadequate nutrition brought about by the low palatability of the diet containing nitrapyrin. These data are supplemental to 025 090169. M. Silva, 4/30/90.

Chronic Study:

** 025 090169 "Nitrapyrin: Chronic (One-Year) Dietary Toxicity Study in Dogs" (Lake Jackson Research Centr, Dow, Project ID: TXT: K-031304-029, 12-27-89). Nitrapyrin technical (Lot #: WP 860516-308B(19B); 92.6% pure) was fed in the diet to beagle dogs at dose levels of 0, 0.5, 3 or 15 mg/kg/day, 4/sex/group. NOEL = 3 mg/kg/day (Hepatotoxicity was exhibited in high dose males and females as increased alkaline phosphatase activity and cholesterol levels. Absolute and relative liver weight was increased and diffuse hypertrophy of hepatocytes was also observed). **No adverse effects. Acceptable**. D. Shimer & M. Silva, 4/5/90.

006, 012 943515, 036148 "Results of Two-Year Dietary Feeding Studies of 6-Chloropicolinic Acid in Beagle Hounds." (2/22/67, Dow) Metabolite, 6-chloropicolinic acid, 98.5%. Three per sex per group were fed 0.02, 0.06 and 0.2% in the diet for 2 years with 1/sex/group sacrificed at 1 year. Initial review (AA, 7/24/85) found unacceptable (dose selection not justified with no overt toxicity reported at high dose, inadequate number of animals, inadequate histopath, no diet analysis.) Subsequent review (Martz, 4/7/86) found study not upgradeable and confirmed that there were positive findings for liver and kidney (degenerative changes at 0.06 and 0.2%). NOEL: 0.02% of diet.

004 943519, Supplemental to 943515, 036148.

003, 008 048112, 019864, Summary information.

ONCOGENICITY, RAT

See combined, rat.

ONCOGENICITY, MOUSE

Subchronic study:

** 350-041; 156914; A Subchronic (3-month) Oral Toxicity Study of Nitrapyrin in the Mouse via Dietary Administration;(I.W. Daly, Pharmaco LSR, Inc., East Millstone, NJ; Report # 93-2278; 5/25/95); Nitrapyrin Technical (90.0 and 92.05%, Lot # WP920415-T19B); 10 mice/sex/dose; dose (mean test substance intake) 0, 200 (M 195.6; F 195.9), 300 (males only) (M 293.7), 400 (M 393.5; F 388.8), 600 (M 541.8; F 515.8), 800 (females only) (F 615.8) mg/kg/day; observations: Numerous mice were found dead or were sacrificed in moribund condition in the two high dose groups (800 mg/kg, F: 9/10; 600 mg/kg, M: 9/10; F: 10/10). Reduced body weights and food consumption was observed at the three highest dose levels. Increased absolute and relative liver weights were seen (M/F 200, 300 and 400 mg/kg). At necropsy enlarged livers were observed at 600 mg/kg (M:7/10; F:6/10). Central to panlobular hepatocellular hypertrophy was observed (M:

200 - 400 mg/kg; F: 200 and 400 mg/kg). Intracytoplasmic vacuoles were seen in hepatocytes(M: 300 - 400 mg/kg; F: 400 mg/kg). Intracellular material (minimal to slight) noted in Kupffer cells and a mixed inflammatory cell infiltrate noted in the livers of numerous 400 mg/kg males and females. Splenic extramedullary hematopoiesis was increased in both sexes (400 mg/kg). The ovaries and uterus were hypoplastic/atrophic (400 mg/kg). Reduced hemoglobin, hematocrit and platelet counts in 400 mg/kg (both sexes); increased reticulocyte, leukocyte and lymphocyte counts (F: 400 mg/kg) and decreased mean platelet counts in the 300 mg/kg males. Statistically significant alterations in several clinical chemistry parameters were seen in primarily the 400 mg/kg dose. NOEL (M/F) = < 200 mg/kg (based on increased absolute and relative liver weights and hepatocellular hypertrophy); **No adverse effects**; **Acceptable.** (Miller, 12/1/97)

Oncogenicity study:

** 029 091273, "Nitrapyrin (N-Serve®): Two-Year Dietary Oncogenicity Study in B6C3F1 Mice", (Quast, J.F., Cosse, P.F. and Corley, R.A., The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI., Study # K-031304-027, 7/23/90), N-SERVE TG (technical grade), AGR-229141, 93.3% nitrapyrin by gas chromatography, fed in the diet for two years to B6C3F1 mice (50/sex/group) at 0 (basal diet), 5, 25, or 75 mg/kg/day. An additional 10 mice/sex/group were included as a satellite group which was sacrificed at 12 months. Chronic NOEL = 5 mg/kg/day (Males showed significantly decreased cholesterol levels at 25 mg/kg and significantly increased serum alanine aminotransferase at 75 mg/kg for the satellite--12 month group. Histopathology showed an increase in staining properties in the duodenum in both sexes at $\geq$ 25 mg/kg/day in both satellite and oncogenicity groups. Liver showed altered cytoplasmic homogeneity in the centrilobular region at $\geq$ 25 mg/kg/day--males or 75 mg/kg/day--females at 12 and 24 months.) Oncogenicity NOEL $\geq$ 75 mg/kg/day (No significant effects were observed.) **No adverse effects** are indicated. **Acceptable**. (H. Green & M. Silva, 5/13/92.)

** 350-042; 156915; “Nitrapyrin (N-Serve Nitrogen Stabilizer): Two-Year Dietary Oncogenicity Study in B6C3F1 Mice” (K.E. Stebbins & P.F. Cosse, Toxicology Research Laboratory, Dow Chemical Co., Midland, MI, Lab. Project Study ID # K-031304-036, 2/27/97). Nitrapyrin (Lot # TSN 100319, 95.4% purity) was administered to 50 B6C3F1 mice/sex/dose in the diet at 0, 125 or 250 mg/kg/day for 2 years. An interim group of 10 mice/sex/dose was included for evaluation of chronic toxicity after 12 months. Mortality for the 0, 125, and 250 mg/kg/day dose groups was 10, 2, and 17 in males and 13, 13, and 10 in females, respectively. Treatment-related reduction (mean of 88 to 97% of control, $p < 0.05$) in body weights were reported in high dose males. Increased absolute and relative liver weights were present at the 12- and 24-month sacrifices in males and females treated at 125 or 250 mg/kg/day. **Possible adverse effects:** Histopathological examination revealed hepatocellular necrosis and associated compensatory hepatocellular proliferation in both sexes at low and high doses. These changes led to the development of an increased frequency of hepatocellular adenomas and/or carcinomas in 250 mg/kg/day high dose males and in low and high dose females. Both sexes treated at 125 and 250 mg/kg/day had an increased incidence of hyperplasia, papillomas, and/or squamous cell carcinomas of the nonglandular mucosa of the stomach. Other histological changes following 12 and 24 months of dosing consisted of vacuolation, hyperplasia and hypertrophy of the mucosal epithelial cells of the duodenum and jejunum in males and females of both treatment groups . NOEL (M/F) = NOAEL (M/F) < 125 mg/kg/day (based on hepatocellular necrosis and adenomas/carcinomas and tumorigenesis of the stomach). Acceptable. (Leung, 12/8/97).

Summary statement:

The earlier study, Record 091273, used doses of 0, 5, 25 and 75 mg/kg/day for two years. The later study, Record 156915, used doses of 0, 125 and 250 mg/kg/day for two years. The first study did not identify any oncogenic effect at doses up to and including 75 mg/kg/day. Gross pathology and histopathology effects were noted in the duodenum (pale mucosa, altered tinctorial properties) at 25 and 75 mg/kg/day. A NOEL of 5 mg/kg/day was determined based on liver and duodenal effects plus clinical chemistry parameters. The authors considered the effects on the duodenum to be “physiologic” in nature and associated with the presence of test material as the mice were not fasted. No toxicologic significance was attached to the duodenal change by the authors. No adverse oncogenic effect was flagged by CDPR in Record 091273.

In the second study at higher doses, tumorigenic effects in the liver and nonglandular stomach were reported. In addition, the second study confirmed the duodenum as a target for chronic effects with a high frequency of vacuolation and hyperplasia in both sexes at both doses. The jejunum also showed these same effects on histological examination at both doses in both sexes. Both tissues showed the effect at the 12-month sacrifice as well as after two years of exposure. The authors state these are “treatment-related histopathologic alterations...” This second study at higher doses indicates the potential for ongogenic effects as well as chronic toxicity to the liver, stomach and intestines. The authors discuss the findings in relationship to the doses, which they consider to have exceeded the maximum tolerated dose (MTD) based on hepatocellular necrosis and proliferation and body weight depression in males. They considered nitrapyrin to be nongenotoxic. The most likely mechanism for hepatocellular tumors was the necrosis with compensatory proliferation over a long period of exposure. In terms of the nonglandular stomach tumors, human stomachs were stated to not have a nonglandular portion and the tumors, therefore, of “...little relevance to man.” Despite these arguments by the authors, the later study was evaluated by DPR as showing a possible adverse tumorigenic and chronic effect. J. Gee. 12/8/97.

REPRODUCTION, RAT

** 023 072241 "Nitrapyrin (N-Serve TG): Results of a Two-Generation Reproduction Study in Fischer 344 Rats," (Health and Environmental Sciences-Texas, Dow Chem. Co., Study ID: TXT:K-031304-025, -025F1, -025FAW, -025FBW, 12-27-88). Nitrapyrin (N-Serve TG; 93.3% pure; LOT #: WP860 516-3088) was fed to Fischer 344 rats in the diet at dose levels of 0, 5, 20 and 75 mg/kg/day for a 2 generation reproduction study, 30/sex/group. NOEL (Adult) = 5 mg/kg/day (Decreased body weight and body weight gain was observed at 75 mg/kg/day in F0 (females) and F1 (both sexes); increased liver and kidney weights (absolute & relative) were observed in F0 males at $\geq$ 20 mg/kg/day and F0 females at 75 mg/kg/day; liver and kidney weights (absolute and relative) were significantly increased in F1 adults of both sexes at $\geq$ 20 mg/kg/day; histopathological effects were observed in F0 & F1 livers of both sexes at $\geq$ 20 mg/kg/day--liver changes included hypertrophy of centrilobular hepatocytes and lipid vacuolation; histopathological effects were observed in kidneys of F0 & F1 males at 75 mg/kg/day which included necrosis of the intratubular epithelium). NOEL (Neonatal) = 20 mg/kg/day (at 75 mg/kg/day, F1 & F2 pup weights were significantly decreased; both sexes of F1 & F2 pups showed enlarged livers, and livers of both sexes had centrilobular vacuolation). NOEL (Reproductive) = 75 mg/kg/day (HDT). **No adverse effects. Acceptable.** M. Silva, 4/6/90.

006 943523 "Results of Fertility and Reproduction Studies in Rats Maintained on Diets Containing 6-Chloropicolinic Acid." (1/16/67, Dow) Metabolite, 6-chloropicolinic acid, 98.5%. Four males and 12 females were fed 0, 0.01, 0.03, or 0.1% in the diet for 3 generations and 3 litters (3rd used for a teratogenicity aspect). The initial review (AA, 7/24/85), found the report unacceptable (inadequate number of animals at risk, doses not justified with no toxicity to adults

at high dose, no histopath of reproductive organs, no individual data, no diet analysis) with possible adverse reproductive effects. A subsequent review found the report to have insufficient information for evaluation. NOEL cannot be determined due to paucity of data. Unacceptable, not upgradeable. (Parker, 4/4/86)

012 036149 Duplicate of 943523.

003, 008 943521, 019865, Summary of 943523.

TERATOLOGY, RAT

Range-finding Studies:

032 130129 "A Range-finding Study to Evaluate the Developmental Toxicity of Nitrapyrin in the Rat," (Schroeder, R.E., Pharmaco LSR, Inc., East Millstone, NJ; Project ID#: 93-4049; 4/14/94). Nitrapyrin technical (92% pure) was administered by gavage to mated Sprague-Dawley CD(SD)BR female rats (10/dose) at 0 (corn oil), 50, 100 and 200 mg/kg during days 6-15 of gestation. **Maternal NOEL =** 50 mg/kg (A slight decrease in maternal body weight gain and food consumption and increased relative weights for liver and kidney were observed at 100 mg/kg. At 200 mg/kg, animals experienced significant decrease in weight, weight gain and food

consumption. Clinical signs were also observed and therefore, the entire dose group was terminated early.) These data are supplemental. M. Silva, 11/7/94.

017 057213 "Nitrapyrin: Oral Teratology Probe Study in Fischer 344 Rats," (Dow Chemical, 5/12/86). Nitrapyrin technical, 91.9%, given by oral gavage to 9 - 10 per group at 0 (corn oil), 15, 50 or 100 mg/kg, days 6 - 15 of gestation with sacrifice on day 16; weight loss/decreased gain at 50 and 100 mg/kg, decreased food consumption at 100 and increased liver weights at 50 and 100 mg/kg with histopathological findings of vacuolation; includes stability and homogeneity data and dosing solution analysis for # 051088; supplemental data for 051088, dose justification, upgrading that study to acceptable status. (Gee, 5/26/88 and Parker, 6/7/88.)

Developmental Toxicity (full studies):

** **033 130131** "A Developmental Toxicity Study in Rats with Nitrapyrin," (Schroeder, R.E., Pharmaco LSR, Inc., East Millstone, NJ; Laboratory study #: 93-4050; 4/14/94). Nitrapyrin technical (92% pure) was administered by gavage to mated female CD(SD)BR rats (28/dose) at 0 (corn oil), 15, 50 and 120 mg/kg during days 6-15 of gestation (mating confirmed = day 0 gestation). **Maternal NOEL =** 15 mg/kg (Dams showed transitory decreased body weight gain at ≥ 50 mg/kg. Food consumption was significantly decreased at 120 mg/kg. There was an increase in emaciation, excessive salivation, alopecia, ano-genital stains and decreased fecal volume at 120 mg/kg. Alopecia in the extremities/snout was increased at ≥ 50 mg/kg. Kidney and liver organ/body weights were significantly increased at 120 mg/kg.) **Developmental NOEL =** 15 mg/kg (Fetal body weights decreased in a dose-related manner--significant in females at 120 mg/kg. There was a significant increase in fetal skeletal malformations at 50 mg/kg (not at 120 mg/kg). An increase in fetal ossification variations was observed at ≥ 50 mg/kg.) **Possible adverse effect for fetal skeletal development was observed.** Acceptable. (M. Silva, 11/14/94).

** 014 051088 "Nitrapyrin: Oral Teratology Study in Fischer 344 Rats," (Dow, 9/18/86).

Nitrapyrin technical, 91.9%, given by gavage on gestation days 6 - 15 at dose levels of 0, 5, 15 or 50 mg/kg/day; maternal and developmental toxicity NOEL $\geq$ 50 mg/kg/day; initially reviewed as unacceptable based on dose selection and lack of dosing analysis (Parker, 2/10/87). With the submission of 017 057213 containing a pilot study for dose justification and also dosing analysis, the study is upgraded to acceptable status. No adverse effect. (Gee, 6/1/88 and Parker, 6/8/88.)

NOTE: In the above acceptable studies, the different NOEL's achieved may be due to several things. The first study was reported in 1986 (Dow Chemical Co.) and was performed in Fischer 344 rats. No maternal or developmental effects were observed at the doses tested (up to 50 mg/kg), however the rangefinding study showed some effects at 50 mg/kg. A subsequent study, performed in 1994 (Pharmaco LSR, Inc.) used CD(SD)BR rats and achieved a NOEL of 15 mg/kg (both maternal & developmental). Therefore, the fact that the studies were performed at different time periods, in different laboratories with different strains of rat may account for the different NOEL's. However, due to the skeletal findings in fetuses in the study performed in 1994 (skeletal findings also observed in rabbits, see 015/051515, below), nitrapyrin must be flagged for induction of developmental effects in rats. M. Silva, 11/15/94.

TERATOLOGY, RABBIT

** 015 051513 "Nitrapyrin: Oral Teratology Study in New Zealand White Rabbits", Dow Mammalian and Environmental Toxicology Research Laboratory, 10/23/85. Nitrapyrin, 91.9% purity, administered by gavage on days 6 - 18 of gestation to groups of 25 - 27 inseminated rabbits at 0 (corn oil), 3, 10 or 30 mg/kg/day. Maternal NOEL = 10 mg/kg/day (**minimal** decrease in body weight gain and increase in liver and kidney weight). Developmental NOEL = 10 mg/kg/day (increased incidence of fetuses with "crooked hyoid"). **No adverse effect**. Initially reviewed as unacceptable and upgradeable (J. Parker, 2/9/87). Submission of Probe study (#057212) and analysis of dosing solutions and individual data allow upgrade to **acceptable**. (Parker, 6/8/88.)

017 057212 "N- Serve: Oral Teratology Probe Study in New Zealand White Rabbits" (Dow Chemical Company, 3/27/85). Nitrapyrin , 92%, given by gavage to 6 - 7 per group inseminated rabbits at 0 (corn oil), 30, 100 or 200 mg/kg/day, days 6 - 18 of gestation with sacrifice on day 19. No dams survived at 100 or 200 mg/kg/day. At 30 mg/kg/day all dams survived and showed enlarged and pale livers and increased kidney and liver weights (absolute and relative). This was submitted as dose justification for study #051513. Analysis of dosing solution and some individual data for #051513 are included in this submission. Supplemental data. (Parker 6/3/88.)

GENE MUTATION

Microbial systems:

006 943524 "Application of the Ames Test for Mutagenesis to Nitrapyrin." (4/8/76, Plant Science Res., Dow) Salmonella strain LT-2, TA1530. Summary. Unacceptable due to insufficient information with no increase in reversion rate reported. No data. No concentrations given. (Apostolou, 7/25/85)

008 019866, Summary information.

** 012 036150 "Study to Determine the Ability of Nitrapyrin to Induce Mutation in Four Histidine-Requiring Strains of Salmonella Typhimurium." (1/18/85, Microtest Res. Ltd., Study no.

DCE 3/S/SR/AF2.) Salmonella strains TA1535, TA97, TA98 and TA100 were tested at 0, 0.8, 4, 20, 100 and 500 ug/plate, based on cytotoxicity study, with and without rat liver activation, in triplicate, two trials. Test run with nitrapyrin technical, no purity stated. Acceptable with no increased reversion rate. (Gee, 3/18/86.)

Mammalian systems:

** 014 051089 "Evaluation of Nitrapyrin in the Chinese Hamster Ovary Cell/Hypoxanthine-Guanine-Phosphoribosyl Transferase (CHO/HGPRT) Forward Mutation Assay." (8/22/86, Dow) Nitrapyrin, 93.4%; tested with and without rat liver activation; -S9, at 0, 20, 40, 60, 80 or 100 ug/ml, 5 plates per concentration, three trials; +S9, at 0, 120, 140,

160, 180 or 200 ug/ml, one trial. No evidence for increase in mutation frequency. Acceptable with minor variations (single trial in activation assay.) (Gee, 2/11/87.)

MUTAGENICITY, CHROMOSOMES

** 012 036152 "Nitrapyrin: Micronucleus Test in Mice." (5/30/85, Microtest) Mouse micronucleus test. Nitrapyrin, 90.64%, sample number 84-2150; given as a single oral dose at 800 mg/kg as MTD; 5/sex/group were given a single oral dose and sacrificed after 24, 48 and 72 hours. Acceptable. No adverse effect reported at 800 mg/kg based on range-finding study. Use of a single high dose (m.t.d.) is acceptable. (Gee, 3/17/86.)

MUTAGENICITY, DNA/OTHER

** 006 943525 "N-Serve TG (Nitrapyrin: 2-chloro-6-(trichloromethyl) pyridine: Evaluation of N-Serve TG in the Rat Hepatocyte Unscheduled DNA Synthesis Assay." (1/5/82, Dow). Nitrapyrin (92% AI) was added to cultures of rat hepatocytes at 1 x 10^{-7} to 1 x 10^{-4} moles/liter, 7 concentrations. Initial review (AA, 7/25/85) found the study unacceptable, with no adverse effects. Subsequent review noted that 2 x 15 or 30 cells were actually examined from 2 slides per concentration; no S-phase blocking is required for hepatocytes and mycoplasma are not a concern in primary cultures; although desireable, few studies use more than one rat per trial and guidelines do not specify a number. No adverse effects, acceptable (Gee, 3/17/86)
012 36151 Exact duplicate of 006 943525.

014 51090 Rebuttal and additional information for 006 943525.

008 19867 Summary information.

NEUROTOXICITY

Not required at this time.